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APPLICATION NUMBER: ***60/144,062***
FILING DATE: ***July 16, 1999***

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Under 35 USC 111(b)

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PROVISIONAL APPLICATION
Under Rule 53(c)

Sir:

(Our Deposit Account No. 03-3975)

Herewith is a PROVISIONAL APPLICATION Our Order No. 41632 (C#) 262675 (M#)

Title: AMINOBENZOPHENONES AS INHIBITORS OF IL-1β AND TNF-α

Atty. Dkt. PMS 262675 (M#) MLA/HEJ/P0799 (Client Ref)

including: Date: July 16, 1999

1. Specification: 23 pages 2. ☐ Specification in non-English language 3. ☐ Drawings: sheet(s)

4. The invention ☐ was ☒ was not made by, or under a contract with, an agency of the U.S. Government.
If yes, Government agency/contact # =

5. ☐ Attached is an assignment and cover sheet. Please return the recorded assignment to the undersigned.

6. ☐ Attached: _____ (No.) Verified Statement(s) establishing "small entity" status under Rules 9 & 27.
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7. ☐ Attached:

8. This application is made by the following named inventor(s) **(Double check instructions for accuracy.):**

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9. NOTE: FOR ADDITIONAL INVENTORS, check box ☐ and attach sheet (PAT102A) with same information regarding additional inventors.

	Larg /Small Entity		Fee Code
10. Filing Fee	$150/$75	+150	114/214
11. If "non-English" box 2 is X'd, add Rule 17(k) processing fee	$130	+0	139
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APPLICATION UNDER UNITED STATES PATENT LAWS

Invention: AMINOBENZOPHENONES AS INHIBITORS OF IL-1β AND TNF-α

Inventor(s): OTTOSEN, Erik Rytter

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This is a:

- ☒ Provisional Application
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- ☐ Substitute Specification
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  Sub. Spec. filed _____
  in App. No. _____ /

SPECIFICATION

P0799ERQurea

AMINOBENZOPHENONES AS INHIBITORS OF IL-1β AND TNF-α

FIELD OF THE INVENTION

This invention relates to a hitherto unknown class of compounds which shows anti-inflammatory effects, to pharmaceutical preparations containing these compounds, to dosage units of such preparations, and to their use in the treatment and prophylaxis of asthma, allergy, arthritis, including rheumatoid arthritis and spondyloarthritis, gout, atherosclerosis, chronic inflammatory bowel disease (Crohn's disease), proliferative and inflammatory skin disorders, such as psoriasis and atopic dermatitis, uveitis, septic shock, AIDS, and acne.

BACKGROUND OF THE INVENTION

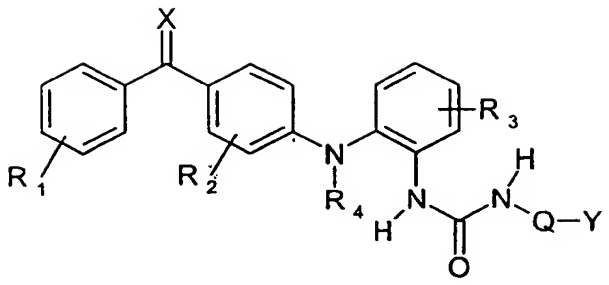
Previously, a series of closely related aminobenzophenones (e.g. 4-(2-amino-4-nitrophenylamino)benzophenone) have been described (Hussein, F.A. *et al*, Iraqi J. Sci., 22, 54-66 (1981)). However, there is no description of their uses. PCT/DK98/00008 discloses aminobenzophenone inhibitors of interleukin 1β (IL-1β) and tumour necrosis factor a (TNF-α) secretion *in vitro*, said compounds being potentially useful for treatment of inflammatory diseases in which the production of cytokines is involved in the pathogenesis, e.g. asthma, rheumatoid arthritis, psoriasis, contact dermatitis, and atopic dermatitis. Furthermore the compounds of PCT/DK98/00008 was tested *in vivo* for anti-inflammatory properties in the 12-*O*-tetradecanoylphorbol-13-acetate (TPA) induced murine chronic skin inflammation model, (De Young, L.M. et al, Agents Actions, 26, 335-341 (1989); Carlson, R.P. et al, Agents Actions, 17, 197-204 (1985); Alford, J.G. et al, Agents Action, 37, (1992); Stanley, P.L. et al, Skin Pharmacol, 4, 262-271 (1991)). In this chronic skin inflammation model the compounds had the same potency compared to the reference compound hydrocortisone.

The purpose of the present invention is to provide further pharmacologically active aminobenzophenone derivatives and related compounds.

This purpose is achieved with the novel aminobenzophenone derivatives according to the general formula I that are potent inhibitors of interleukin 1β (IL-1β) and tumour necrosis factor α (TNF-α) secretion *in vitro*, making them potentially useful for treatment of inflammatory diseases, in which the secretion and regulation of cytokines or more specifically interleukin 1β (IL-1β) and tumour necrosis factor α (TNF-α) are involved in the pathogenesis. The inhibition or down regulation of the cytokines is possibly due to an inhibition of MAP kinases.

SUMMARY OF THE INVENTION

The compounds of the present invention are represented by the general formula I below



I

wherein R_1 represents one or more, same or different substituents selected from the group consisting of halogen, hydroxy, mercapto, trifluoromethyl, amino, $(C_1$-$C_3)$alkyl, $(C_2$-$C_3)$olefinic group, $(C_1$-$C_3)$alkoxy, $(C_1$-$C_3)$alkylthio, $(C_1$-$C_6)$alkylamino, $(C_1$-$C_3)$alkoxycarbonyl, cyano, carbamoyl, phenyl, and nitro;

R_2 represents one or more, same or different substituents selected from the group consisting of halogen, hydroxy, mercapto, trifluoromethyl, amino, $(C_1$-$C_3)$alkyl, $(C_2$-$C_3)$olefinic group, $(C_1$-$C_3)$alkoxy, $(C_1$-$C_3)$alkylthio, $(C_1$-$C_6)$alkylamino, $(C_1$-$C_3)$alkoxycarbonyl, cyano, carbamoyl, phenyl, and nitro;

R_3 represents hydrogen, halogen, hydroxy, mercapto, trifluoromethyl, amino, $(C_1$-$C_3)$alkyl, $(C_2$-$C_3)$olefinic group, $(C_1$-$C_3)$alkoxy, $(C_1$-$C_3)$alkylthio, $(C_1$-$C_6)$alkylamino, $(C_1$-$C_3)$alkoxycarbonyl, phenyl, cyano, carboxy, or carbamoyl;

R_4 represents hydrogen, $(C_1$-$C_3)$alkyl, or allyl;

Q represents a bond, $-SO_2-$, or $-C(R_6)(R_7)(-O-C=O)-$, in which formula R_6 and R_7 independently represent hydrogen, trifluoromethyl, or $(C_1$-$C_4)$alkyl;

Y represents $(C_1$-$C_{15})$alkyl, $(C_2$-$C_{15})$olefinic group, $(C_3$-$C_{10})$carbocyclic group, or phenyl, any of which is optionally substituted by one or more, same or different substituents represented by the formula R_5; or Y represents a group of formula $-(Z\text{-}O)_n\text{-}Z$, where Z is a $(C_1$-$C_3)$alkyl and n is an integer > 1, and no continuous linear sequence of atoms in the group Y exceeds 15;

R_5 represents halogen, hydroxy, mercapto, trifluoromethyl, $(C_1$-$C_4)$alkyl, amino, $(C_1$-$C_3)$alkoxy, $(C_1$-$C_3)$alkylthio, $(C_1$-$C_6)$alkylamino, $(C_1$-$C_3)$alkoxycarbonyl, cyano, azido, nitro, -COOH, $-CONH_2$, -CONHR', or -CONRR' wherein R and R' stands for $(C_1$-$C_3)$alkyl;

X represents oxygen or sulphur,

or a pharmaceutically acceptable salt thereof, or a hydrate or solvate thereof.

DETAILED DESCRIPTION OF THE INVENTION

Preferred embodiments of the invention:

In compounds of the invention it is preferred that R_1 represents one or more, same or different substituents selected from the group consisting of fluoro, chloro, bromo, hydroxy, trifluoromethyl, amino, $(C_1$-$C_2)$alkyl, $(C_2$-$C_3)$alkenyl, $(C_1$-$C_3)$alkoxy, $(C_1$-$C_3)$alkoxycarbonyl, or cyano; R_2 represents one or more, same or different substituents selected from the group consisting of hydrogen, fluoro, chloro, bromo, hydroxy, trifluoromethyl, amino, $(C_1$-$C_2)$alkyl, $(C_2$-$C_3)$alkenyl, $(C_1$-$C_3)$alkoxy; R_3 represents one or more, same or different substituents selected from the group consisting of hydrogen, fluoro, chloro, bromo, hydroxy, trifluoromethyl, $(C_1$-$C_3)$alkyl, $(C_2$-$C_3)$alkenyl, $(C_1$-$C_3)$alkoxy, $(C_1$-$C_3)$alkoxycarbonyl, cyano, or carboxy; R_4 represents hydrogen, $(C_1$-$C_2)$alkyl, or allyl; X represents oxygen; Q represents a bond. or $-SO_2-$; Y represents $(C_1$-$C_6)$alkyl; $(C_2$-$C_6)$alkenyl; $(C_3$-$C_6)$cycloalkyl; $(C_5$-$C_8)$cycloalkene group; or phenyl; any of which is optionally substituted by one or more, same or different substituents selected from the group consisting of the formula R_5 as defined below, and R_5 represents fluoro, chloro, bromo, hydroxy, amino, $(C_1$-$C_2)$alkoxy, $(C_1$-$C_4)$alkylamino, $(C_1$-$C_3)$alkoxycarbonyl, cyano, azido, -COOH, $-CONH_2$, -CONHR', or -CONR'R' wherein R' represents $(C_1$-$C_2)$alkyl.

More preferred are compounds of formula I wherein R_1 represents one or more, same or different substituents selected from the group consisting of fluoro, chloro, bromo, hydroxy, methyl, or methoxy; preferably R_1 is methyl and most preferrably 2-methyl; R_2 represents one or more, same or different substituents selected from the group consisting of hydrogen, fluoro, chloro, bromo, hydroxy, methyl, or methoxy; preferably R_2 is Cl and most preferably 2-Cl; preferably R_3 represents hydrogen, methyl, methoxy, fluoro, chloro, or bromo; R_4 represents hydrogen; Y represents $(C_1$-$C_6)$alkyl, $(C_3$-$C_7)$cycloalkyl, or phenyl; any of which may be optionally substituted by one or more, same or different substituents selected from the group consisting of fluoro, chloro, bromo, hydroxy, amino, azido, $(C_1$-$C_3)$alkyl, $(C_1$-$C_2)$alkoxycarbonyl, cyano, -COOH, $-CONH_2$, and $CON(CH_3)_2$. Most preferably Y represents methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, cyclohexyl, hexyl, 6-chloro-hexyl, $-(CH_2)_2COOCH_2CH_3$, $(CH_2)_2COOH$, tolyl, or phenyl.

Further preferred compounds of general formula I are compounds wherein R_1, R_2, and R_3 represent

one substituent. R_1 and R_2 preferably being in the ortho position.

Specific compounds of the invention includes:
1-Cyclohexyl-3-[2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]urea (Compound 101),
1-Ethyl-3-[2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]urea (Compound 102),
1-[2-[3-Chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]-3-phenylurea (Compound 103),
1-Butyl-3-[2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]urea (Compound 104),
1-[2-[3-Chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]-3-(4-methylphenylsulfonyl)urea (Compound 105),
1-[2-[3-Chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]-3-(phenylsulfonyl)urea (Compound 106),
1-*tert*-Butyl-3-[2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]urea (Compound 107),
1-[2-[3-Chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]-3-*iso*-propylurea (Compound 108),
1-[2-[3-Chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]-3-propylurea (Compound 109),
1-Methyl-3-[2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]urea (Compound 110),
Ethyl 3-[2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]ureido)propionate (Compound 111),
1-Ethyl-3-[5-bromo-2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]urea (Compound 112),
3-[2-[3-Chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]ureido)propionic acid (Compound 113),
1-Ethyl-3-[2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]-5-fluoro-phenyl]urea (Compound 114),
and salts thereof with pharmaceutically acceptable acids, hydrates or solvates thereof.

As used in the specification, unless specified to the contrary, the following terms have the meaning indicated:

"Alkyl" refers to any univalent group derived from an alkane by removal of a hydrogen atom from any carbon atom, and includes the subclasses of normal alkyl (*n*-alkyl), and primary, secondary and tertiary alkyl groups respectively, and having the number of carbon atoms specified, including for example (C_1-C_3)alkyl, (C_1-C_4)alkyl, (C_5)alkyl, (C_5-C_{15})alkyl, (C_6-C_{10})alkyl, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, and t-butyl. Alkane refers to an acyclic branched or unbranched hydrocarbon having the general formula C_nH_{2n+2}, and therefore consisting entirely of hydrogen atoms and saturated carbon atoms.

"Olefinic group" refers to a straight or branched acyclic hydrocarbon having one or more carbon-carbon double bonds of either E or Z stereochemistry where applicable, and having the number of carbon atoms specified. The term includes, for example, (C_2-C_{15})olefinic group, preferably a (C_2-C_{15})alkenyl; (C_2-C_3)olefinic group, preferably a (C_2-C_3)alkenyl; vinyl; allyl; 1- butenyl; 2-butenyl; and 2-methyl-2-propenyl. Olefinic groups having only one carbon-carbon double bond, herein called alkenyl, are preferred.

"Alkoxy" refers broadly to a radical of the formula -OR, where R is alkyl as defined above, for example $(C_1$-$C_3)$alkoxy, $(C_1$-$C_2)$alkoxy, methoxy, ethoxy, n-propoxy, and the like.

"$(C_1$-$C_3)$alkylthio" refers broadly to a radical of the formula -SR, where R is alkyl as defined above and includes methylthio, ethylthio, n-propylthio, and 2-propylthio.

"$(C_1$-$C_6)$alkylamino" refers broadly to a radical of the formula -NHR or $-NR_2$, where R is alkyl as defined above having from 1-6 carbon atoms and includes, for example, methylamino, dimethylamino, di-(n-propyl)amino, and n-butyl(ethyl)amino.

"$(C_1$-$C_3)$alkoxycarbonyl" refers broadly to a radical of the formula -COOR, where R is alkyl as defined above and includes methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, and i-propoxycarbonyl.

"$(C_3$-$C_{10})$monocyclic hydrocarbon group" includes the saturated cycloalkanes and unsaturated cyclic olefins, such as cycloalkenes having one endocyclic double bond, and having from 3-10 carbon atoms, and includes, for example, $(C_3$-$C_8)$cycloalkyl, cyclopropyl, cyclopentyl, cyclohexyl, and cyclooctyl, $(C_3$-$C_{10})$cycloalkene group, and $(C_3$-$C_8)$cycloalkene group. Specific examples are cycloprop-2-enyl, cyclobut-2-enyl, cyclopent-2-enyl, cyclohex-3-enyl, and cyclonon-4-enyl.

"Amino" means the group $-NH_2$.

"Carbamoyl" refers to any one of the groups $-CONH_2$, -CONHR, and -CONRR' where R and R' represent alkyl as defined above.

"Carboxy" refers to a radical of the formula -COOH.

"Halogen" means the same or different of fluoro, chloro, bromo, and iodo; fluoro, chloro, and bromo being preferred.

The phenyl group of R_1 and R_2 may optionally be substituted, e.g. with hydroxy; amino; nitro; cyano; halogen, preferably fluoro, chloro, or bromo; methyl; or methoxy.

The compounds can be used in the form of their salts which are formed with pharmaceutically acceptable inorganic or organic acids, such as hydrochloric, hydrobromic and hydroiodic acid, phosphoric acid, sulphuric acid, nitric acid, p-toluenesulphonic acid, methanesulphonic acid, formic acid, acetic acid propionic acid, citric acid, tartaric acid, succinic acid, benzoic acid, maleic acid, these examples being considered as non-limiting for the invention.

Pharmacological methods

To study the effect of the compound of the present invention in vitro the inhibition of the IL-1β and TNF-α secretion was measured using the following procedure:

Cytokine production was measured in the media from lipopolysaccharide (LPS) stimulated peripheral blood mononuclear cells. The mononuclear cells were isolated from human peripheral blood by Lymphoprep® (Nycomed, Norway) fractionation and suspended in RPMI 1640 (growth medium) with foetal calv serum (FCS, 2%), at a concentration of 5×10^5 cells/ml. The cells were incubated in 24-well tissue culture plates in 1 ml aliquots. Test compounds were dissolved in dimethylsulfoxide (DMSO, 10 mM) and were diluted with the medium. Compounds were added to the cells for 30 minutes, then LPS (1 mg/ml final concentration) was added. The plates were incubated for 18 hours, and the concentration of IL-1β and TNF-α in the medium was determined by enzyme-linked immunosorbent assays. The median inhibitory concentrations (IC_{50}) of the compounds were calculated. The results are shown in Table 1 below.

The compounds of the present invention also show similar activities in the ability to inhibit PMN (polymorphonuclear) superoxide secretion which is also indicative of potentially useful anti-inflammatory drugs. The compounds were tested using the following procedure:

Human polymorphonuclear (PMN) granulocytes were isolated from human blood by dextran sedimentation, Lymphoprep® fractionation and hypotonic lysis of contaminating erythrocytes.

Superoxide anion generation was measured as the superoxide dismutase inhibitable reduction of ferricytochrome C (Madhu, S.B. et al, Inflammation, 16, 241, (1992)). The cells were suspended in Hanks' balanced salt solution, and incubated for 10 minutes at 37°C with test compounds. The cells were primed by the addition of TNF-α (3 ng/ml final concentration) for 10 minutes, and then ferricytochrome C, (final concentration 750µg/ml), bovine serum albumin (BSA, final concentration 1 mg/ml) and formyl-methionyl-leucyl-phenylalanine (fMLP, final concentration 10^{-7} M) were added for 3 minutes. The cells were chilled on ice, and were spun down. The optical densities in the cell-free supernatant was measured in a spectrophotometer. The median inhibitory concentration (IC_{50}) of the compounds was calculated. The results are shown in Table 1.

Table 1. Inhibition of cytokines and PMN-superoxide production in vitro by compounds of the present invention.

Comp No.; Ex. No.	The median inhibition concentration (IC_{50}, nM) of IL-1β	TNF-α	PMN-superoxide
101, Ex. 1	13	5.0	4.0
102, Ex. 2	22	2.2	13
114, Ex. 3	7.9	3.2	4.0
ref. a)	13	7.1	5.0
ref. b)	>1000	631	316

ref. a): 4-(2-Aminophenylamino)-2-chloro-2'-methylbenzophenone, compound 106 disclosed in PCT/DK98/00008. ref. b): 1-Ethyl-3-[2-(4-benzoyl-phenylamino)phenyl]urea of the general formula I in PCT/DK98/00008.

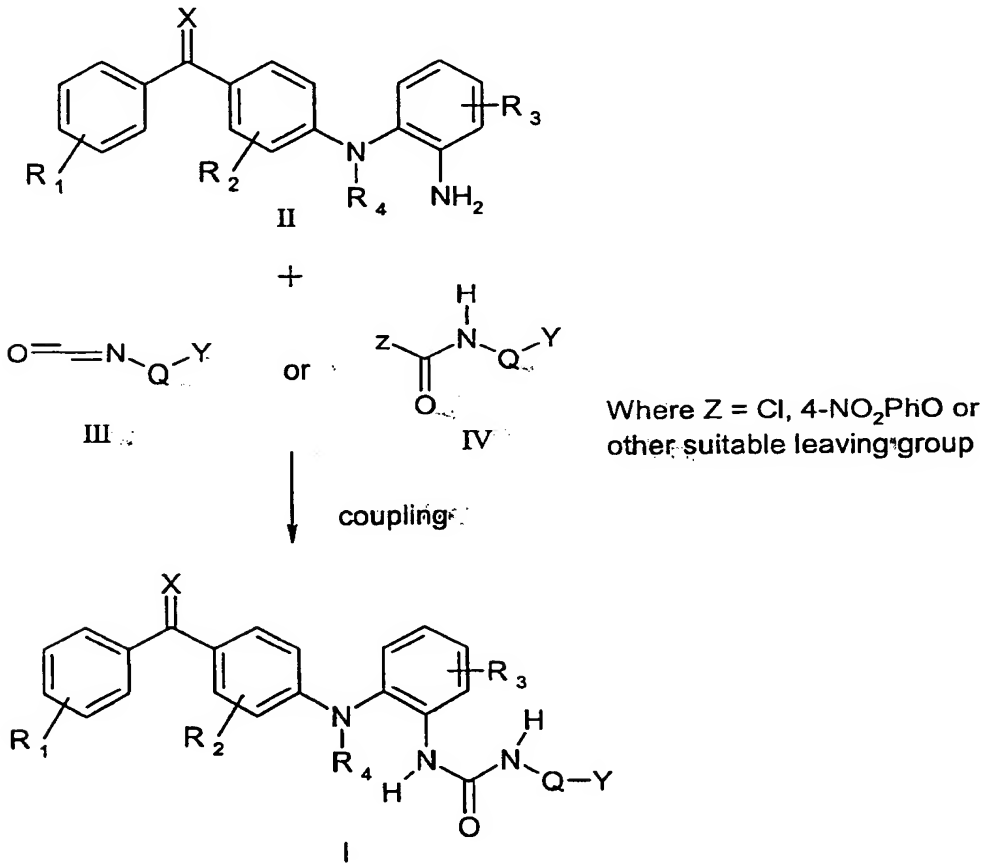
These results show that the compounds of the present invention are able to inhibit the production of IL-1β, TNF-α and PMN-superoxide showing pharmacological activities comparable to compounds of the prior art, thus making them potentially useful in the treatment of inflammatory diseases.

To study the compounds of the present invention *in vivo* the 12-O-tetradecanoylphorbol-13-acetate (TPA) induced murine chronic skin inflammation model can be used (De Young, L.M. et al, Agents Actions, 26, 335-341 (1989); Carlson, R.P. et al, Agents Actions, 17, 197-204 (1985); Alford, J.G. et al, Agents Action, 37, (1992); Stanley, P.L. et al, Skin Pharmacol, 4, 262-271 (1991)), cf. description of method in PCT/DK98/00008 hereby incorporated by reference. These results shows that the compounds of the present invention are of the same potency compared to known reference compounds, e.g. hydrocortisone with its known side effects, whereas the compounds of the present invention are well tolerated and are non-toxic. Some members of the present class of compounds show a very low absorption, thus making them especially useful in the treatment of various dermatological diseases. In general, they may be administered by e.g. oral, intravenous, intranasal, topically or transdermal routes.

Method of preparation

The compounds of the present invention can be prepared in a number of ways well known to those skilled in the art of organic synthesis. The compounds of the present invention can be synthesised using the methods outlined below, together with methods known in the art of synthetic organic chemistry, or variations thereof as appreciated by those skilled in the art. Preferred methods include, but are not limited to, those described below. The novel compounds of formula I may be prepared using the reactions and techniques described in this section. The reactions are performed in solvents appropriate to the reagents and materials employed and are suitable for the transformations being effected. Also, in

the synthetic methods described below, it is to be understood that all proposed reaction conditions, including choice of solvent, reaction atmosphere, reaction temperature, duration of experiment and work-up procedures, are chosen to be conditions of standard for that reaction, which should be readily recognised by one skilled in the art. It is understood by one skilled in the art of organic synthesis that the functionality present on various portions of the educt molecule must be compatible with the reagents and reactions proposed. Not all compounds of formula I falling into a given class may be compatible with some of the reaction conditions required in some of the methods described. Such restrictions to the substituents which are compatible with the reaction conditions will be readily apparent to one skilled in the art and alternate methods can be used.



Scheme 1

Compounds according to the present invention may be prepared by a process comprising coupling of an amine of the formula II with an isocyanates of the formula III or a suitable activated derivative with the formula IV; e.g. carbamic acid chlorides and carbamic acid esters (phenoxy, 4-nitrophenoxy and 2,4,5-trichlorophenoxy) or other suitable activated derivatives of the formula IV, as shown in scheme 1, where R_1, R_2, R_3, R_4, Q, X, and Y are as defined in general formula I, except that any substituents or functional group which are potentially reactive in the coupling reaction may themselves be protected

before the coupling reaction is performed and subsequently removed.

The present compounds are intended for use in pharmaceutical compositions which are useful in the treatment of the above mentioned diseases.

The amount required of a compound of formula I (hereinafter referred to as the active ingredient) for therapeutic effect will, of course, vary both with the particular compound, the route of administration and the mammal under treatment. A suitable dose of a compound of formula I for systemic treatment is 0.1 to 200 mg/kg bodyweight, the most preferred dosage being 0.2 to 50 mg/kg of mammal bodyweight, administered one or more times daily.

While it is possible for an active ingredient to be administered alone as the raw chemical, it is preferable to present it as a pharmaceutical formulation. Conveniently, the active ingredient comprises from 0.1% to 100% by weight of the formulation.

Conveniently, dosage units of a formulation contain between 0.07 mg and 1 g of the active ingredient. For topical administration, the active ingredient preferably comprises from 1% to 20% by weight of the formulation but the active ingredient may comprise as much as 50% w/w. Formulations suitable for nasal or buccal administration may comprise 0.1% to 20% w/w. for example about 2% w/w of active ingredient.

By the term "dosage unit" is meant a unitary, i.e. a single dose which is capable of being administered to a patient, and which may be readily handled and packed, remaining as a physically and chemically stable unit dose comprising either the active material as such or a mixture of it with solid or liquid pharmaceutical diluents or carriers.

The formulations, both for veterinary and human medical use, of the present invention comprise an active ingredient in association with a pharmaceutically acceptable carrier therefore and optionally other therapeutic ingredient(s). The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulations and not deleterious to the recipient thereof.

The formulations include those in a form suitable for oral, ophthalmic, rectal, parenteral (including subcutaneous, intramuscular and intravenous), transdermal, intra-articular, topical, nasal, or buccal administration.

The formulations may conveniently be presented in dosage unit form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active ingredient into association with the carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carri r or both, and then, if necessary, shaping the product into

th desired formulation.

Formulations of the present invention suitabl for oral administration may be in the form of discrete units as capsules, sachets, tablets or lozenges, each containing a predetermined amount of the active ingredient; in the form of a powder or granules; in the form of a solution or a suspension in an aqueous liquid or non-aqueous liquid; or in the form of an oil-in-water emulsion or a water-in-oil emulsion. The active ingredient may also be administered in the form of a bolus, electuary or paste.

Formulations for rectal administration may be in the form of a suppository incorporating the active ingredient and a carrier such as cocoa butter, or in the form of an enema.
Formulations suitable for parenteral administration conveniently comprise a sterile oily or aqueous preparation of the active ingredient which is preferably isotonic with the blood of the recipient.

Formulations suitable for intra-articular administration may be in the form of a sterile aqueous preparation of the active ingredient which may be in microcrystalline form, for example, in the form of an aqueous microcrystalline suspension. Liposomal formulations or biodegradable polymer systems may also be used to present the active ingredient for both intra articular and ophthalmic administration.

Formulations suitable for topical administration, including eye treatment, include liquid or semi-liquid preparations such as liniments, lotions, gels, applicants, oil-in-water or water-in-oil emulsions such as creams, ointments or pastes; or solutions or suspensions such as drops.

Formulations suitable for administration to the nose or buccal cavity include powder, self-propelling and spray formulations, such as aerosols and atomizers.
In addition the aforementioned ingredients, the formulations of this invention may include one or more additional ingredients.

The compositions may further contain other therapeutically active compounds usually applied in the treatment of the above mentioned pathological conditions, for instance glucocorticoids, vitamin D's, antihistamines, platelet activating factor (PAF) antagonists, anticolinergic agents, methyl xanthines, β-adrenergic agents, salicylates, indomethacin, flufenamate, naproxen, timegadine, gold salts, penicillamine, serum cholesterol-reducing agents, retinoids, zinc salts, and salicylazosulfapyridin (Salazopyrin).

The novel compounds of the invention are of value in the human and veterinary practice as systemic and topical therapeutic agents for the treatment and prevention of diseases. The novel compounds show anti-acne properties and, i.a., anti-inflammatory and cytokine regulating effects possibly due to MAP kinase inhibition, and are useful in the treatment and prophylaxis of asthma, allergy, arthritis, including rheumatoid arthritis and spondyloarthritis, gout, atherosclerosis, chronic inflammatory bowel

disease (Crohn's disease), proliferative and inflammatory skin disorders, such as psoriasis, atopic dermatitis, uveitis, septic shock, AIDS, and osteoporosis.

The invention will now be further described in the following non-limiting general procedures, preparations and examples:

EXAMPLES

General procedures, preparations and examples

The exemplified compounds I are listed in table 2. All melting points are uncorrected. For ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra (300 MHz) chemical shift values (δ) (in ppm) are quoted, unless otherwise specified, for deuteriochloroform and hexadeuterodimethylsulfoxide solutions relative to internal tetramethylsilane (δ 0.00) or chloroform (^{1}H NMR δ 7.25, ^{13}C NMR δ 76.81). The value for a multiplet (m), either defined (doublet (d), triplet (t), quartet (q)) or not at the approximate mid point is given unless a range is quoted (s singlet, b broad). The organic solvents used were anhydrous. The term "chromatography" refers to column chromatography using the flash technique and was performed on silica gel.

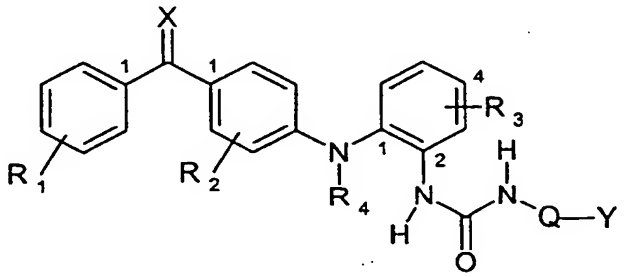
The following abbreviations have been used througout:

AgOAc	Silver acetate
BTC	Bis(trichloromethyl) carbonate
$CDCl_3$	Deuteriochloroform
DMF	*N*,*N*-Dimethylformamide
DMSO-d_6	Hexadeuterodimethylsulfoxide
Et_3N	Triethylamine
EtOAc	Ethyl acetate
Et_2O	Diethylether
HMPA	Hexamethylphosphorous triamide
NMM	*N*-Methylmorpholine
THF	Tetrahydrofurane
TLC	Thin layer chromatography

Table 2 Compounds of general formula I

Comp. No.	Example No.	X	R_1	R_2	R_3	R_4	Q	Y
101	1	O	2-Me	2-Cl	H	H	Bond	-cyclohexyl
102	2	O	2-Me	2-Cl	H	H	Bond	$-CH_2CH_3$
103	3	O	2-Me	2-Cl	H	H	Bond	-phenyl
104	4	O	2-Me	2-Cl	H	H	Bond	$-(CH_2)_3CH_3$
105	5	O	2-Me	2-Cl	H	H	$-(SO_2)-$	-tolyl
106	6	O	2-Me	2-Cl	H	H	$-(SO_2)-$	-phenyl
107	7	O	2-Me	2-Cl	H	H	Bond	$-C(CH_3)_3$
108	8	O	2-Me	2-Cl	H	H	Bond	$-CH(CH_3)_2$
109	9	O	2-Me	2-Cl	H	H	Bond	$-(CH_2)_2CH_3$
110	10	O	2-Me	2-Cl	H	H	Bond	$-CH_3$
111	11	O	2-Me	2-Cl	H	H	Bond	$-(CH_2)_2COOCH_2CH_3$
112	12	O	2-Me	2-Cl	4-Br	H	Bond	$-CH_2CH_3$
113	13	O	2-Me	2-Cl	H	H	Bond	$-(CH_2)_2COOH$
114	14	O	2-Me	2-Cl	4-F	H	Bond	$-CH_2CH_3$

The numbering in Table 2 refers to the numbering in the formula below:



General procedure 1: Coupling of compounds of the general formula II with compounds of the general formula III to give compounds of the general formula I, or a protected derivative thereof.

To a solution or suspension of an amine (1.0 mmol), with the general formula II, in an inert solvent (10 ml, typically toluene, pyridine or EtOAc) was slowly added an isocyanate (1.1-2.5 mmol), with the general formula III. Stirring was continued at room temperature for 24 h or until the starting material had disappeared as seen on TLC. The reaction mixture was concentrated *in vacuo* to afford the crude

product. The crude product was typically either purified by chromatography and/or crystallized to give the title compound.

Example 1

1-Cyclohexyl-3-[2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]urea (Compound 101)

General procedure: 1

Starting compound II: 4-(2-Aminophenylamino)-2-chloro-2'-methylbenzophenone

Starting compound III: Cyclohexyl isocyanate

Solvent for the reaction: EtOAc

Purification: Chromatography using EtOAc/hexane 1:1 as eluant followed by trituration from Et_2O

Mp: 154-155 °C

^{1}H NMR (DMSO-d_6): δ 8.34 (s,1H), 8.05 (d,1H), 7.76 (s,1H), 7.41 (m,1H), 7.35-7.10 (m,6H), 6.95 (m,1H), 6.68 (m,2H), 6.57 (m,1H), 3.44 (m,1H), 2.29 (s,3H), 1.77 (m,2H), 1.63 (m,2H), 1.52 (m,1H), 1.40-1.00 (m,5H)

Example 2

1-Ethyl-3-[2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]urea (Compound 102)

General procedure: 1

Starting compound II: 4-(2-Aminophenylamino)-2-chloro-2'-methylbenzophenone

Starting compound III: Ethyl isocyanate

Solvent for the reaction: Pyridine

Purification: The title compound crystallized on the addition of water to the reaction mixture. Filtration, washing (water), and drying afforded a pure crystalline product.

Mp: 158.3-159.8 °C

^{1}H NMR (DMSO-d_6): δ 8.34 (s,1H), 8.04 (d,1H), 7.79 (s,1H), 7.42 (m,1H), 7.10-7.34 (m,6H), 6.96 (m,1H), 6.67 (m,2H), 6.57 (m,1H), 3.07 (m,2H), 2.29 (s,3H), 1.02 (t,3H)

Example 3

1-[2-[3-Chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]-3-phenylurea (Compound 103)

General procedure: 1, except the reaction mixture was heated to 100 °C for 4 h

Starting compound II: 4-(2-Aminophenylamino)-2-chloro-2'-methylbenzophenone

Starting compound III: Phenyl isocyanate

Solvent for the reaction: Pyridine

Purification: Crystallization from Et_2O

Mp: 163-166.8 °C

^{1}H NMR (DMSO-d_6): δ 9.15 (s,1H), 8.43 (s,1H), 8.13 (s,1H), 8.09 (d,1H), 7.10-7.50 (m,11H), 7.05

(m,1H), 6.96 (m,1H), 6.75 (d,1H), 6.63 (dd,1H), 2.28 (s,3H)

Exampl 4

1-Butyl-3-[2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]urea (Compound 104)

General procedure: 1, except the reaction mixture was heated to 100 °C for 4 h

Starting compound II: 4-(2-Aminophenylamino)-2-chloro-2'-methylbenzophenone

Starting compound III: Butyl isocyanate

Solvent for the reaction: Toluene

Purification: Chromatography using EtOAc/pentane 3:7 as eluant followed by crystallization from Et_2O

Mp: 104-106 °C

^1H NMR (DMSO-d_6): δ 8.35 (s,1H), 8.04 (d,1H), 7.80 (s,1H), 7.41 (m,1H), 7.08-7.34 (m,6H), 6.97 (m,1H), 6.70 (t,1H), 6.66 (d,1H), 6.57 (dd,1H), 3.05 (m,2H), 2.29 (s,3H), 1.20-1.40 (m,4H), 0.86 (t,3H)

Example 5

1-[2-[3-Chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]-3-(4-methylphenylsulfonyl)urea (Compound 105)

General procedure: 1

Starting compound II: 4-(2-Aminophenylamino)-2-chloro-2'-methylbenzophenone

Starting compound III: p-Toluenesulfonyl isocyanate

Solvent for the reaction: Toluene

Purification: The product was filtered off and washed with Et_2O to afford the title compound.

Mp: 180-185 °C

^{13}C NMR (DMSO-d_6): δ 195.3, 150.3, 149.0, 143.9, 139.1, 136.7, 136.4, 133.9, 133.4, 133.4, 131.0, 130.7, 129.5, 129.3, 129.2, 128.8, 127.2, 126.4, 126.3, 125.6, 125.5, 124.1, 120.5, 114.7, 111.4, 20.9, 19.7

Example 6

1-[2-[3-Chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]-3-(phenylsulfonyl)urea (Compound 106)

General procedure: 1

Starting compound II: 4-(2-Aminophenylamino)-2-chloro-2'-methylbenzophenone

Starting compound III: Benzenesulfonyl isocyanate

Solvent for the reaction: Toluene

Purification: The product was filtered off and washed with Et_2O to afford the title compound.

Mp: 196-201 °C

^{13}C NMR (DMSO-d_6): δ 195.3, 150.3, 139.6, 139.1, 136.4, 133.8, 133.7, 133.4, 131.7, 131.0, 130.7, 130.3, 129.3, 129.0, 128.8, 128.4, 127.2, 126.4, 126.4, 125.6, 125.5,

124.1, 120.5, 116.3, 114.7, 111.4, 19.7

Exampl 7

1-*tert*-Butyl-3-[2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]urea (Compound 107)

General procedure: 1, except the reaction mixture was heated to 50 °C for 6 h

Starting compound II: 4-(2-Aminophenylamino)-2-chloro-2'-methylbenzophenone

Starting compound III: *tert*-Butyl isocyanate

Solvent for the reaction: Pyridine

Purification: The title compound crystallized on the addition of water to the reaction mixture. Filtration, washing (water), and drying afforded a pure crystalline product.

Mp: 159-161 °C

^{1}H NMR (DMSO-d_6): δ 8.32 (s,1H), 8.05 (d,1H), 7.73 (s,1H), 7.07-7.46 (m,7H), 6.95 (m,1H), 6.67 (d,1H), 6.60 (s,1H), 6.57 (dd,1H), 2.29 (s,3H), 1.26 (s,9H)

Example 8

1-[2-[3-Chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]-3-*iso*-propylurea (Compound 108)

General procedure: 1

Starting compound II: 4-(2-Aminophenylamino)-2-chloro-2'-methylbenzophenone

Starting compound III: *iso*-Propyl isocyanate

Solvent for the reaction: Toluene

Purification: Chromatography using EtOAc/pentane 3:7 as eluant followed by crystallization from water

Mp: 103-106 °C

^{1}H NMR (DMSO-d_6): δ 8.34 (s,1H), 8.07 (d,1H), 7.74 (s,1H), 7.42 (m,1H), 7.10-7.35 (m,6H), 6.95 (m,1H), 6.66 (m,2H), 6.56 (dd,1H), 3.71 (m,1H), 2.29 (s,3H), 1.06 (d,6H)

Example 9

1-[2-[3-Chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]-3-propylurea (Compound 109)

General procedure: 1

Starting compound II: 4-(2-Aminophenylamino)-2-chloro-2'-methylbenzophenone

Starting compound III: Propyl isocyanate

Solvent for the reaction: Pyridine

Purification: Crystallization from Et_2O

Mp: 133-135 °C

^{13}C NMR (DMSO-d_6): δ 195.2, 155.1, 150.7, 139.4, 136.3, 136.2, 133.5, 130.9, 130.5, 128.6, 128.3, 126.1, 125.8, 125.5, 121.8, 120.3, 114.7, 111.4, 40.8, 22.8, 19.6, 11.3

Example 10

1-Methyl-3-[2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]urea (Compound 110)

General procedure: 1

Starting compound II: 4-(2-Aminophenylamino)-2-chloro-2'-methylbenzophenone

Starting compound III: Methylisocyanate

Solvent for the reaction: Pyridine

Purification: Crystallization from Et_2O

Mp: 154-155 °C

^1H NMR (DMSO-d_6): δ 8.35 (s,1H), 8.01 (d,1H), 7.84 (s,1H), 7.40 (m,1H), 7.09-7.35 (m,6H), 6.97 (m,1H), 6.68 (d,1H), 6.59 (m,2H), 2.61 (d,3H), 2.29 (s,3H)

Example 11

Ethyl 3-[2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]ureido)propionate (Compound 111)

General procedure: 1

Starting compound II: 4-(2-Aminophenylamino)-2-chloro-2'-methylbenzophenone

Starting compound III: Ethyl 3-isocyanatopropionate

Solvent for the reaction: Pyridine

Purification: Chromatography using EtOAc/pentane 3:2 as eluant to give the title compund as a syrupy

^{13}C NMR ($CDCl_3$): δ 196.7, 172.9, 156.3, 148.8, 139.2, 137.8, 135.0, 133.6, 133.0, 131.9, 131.3, 130.9, 129.6, 128.5, 125.4, 125.4, 124.2, 123.8, 116.4, 112.7, 60.9, 36.0, 34.7, 20.4, 14.1

Example 12

1-Ethyl-3-[5-bromo-2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]urea (Compound 102)

General procedure: 1

Starting compound II: 4-[(2-Amino-4-bromo-phenyl)amino]-2-chloro-2'-methylbenzophenone

Starting compound III: Ethyl isocyanate

Solvent for the reaction: Pyridine

Purification: Crystallization from a mixture of EtOAc/pentane 1:1

Mp: 125-127 °C

^{13}C NMR ($CDCl_3$): δ 197.5, 155.8, 149.2, 138.9, 137.7, 135.2, 135.0, 133.6, 131.4, 131.2, 129.8, 129.7, 128.2, 126.8, 126.2, 125.5, 125.0, 118.7, 116.1, 112.3, 35.2, 20.5, 15.2

Example 13

3-[2-[3-Chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]ureido)propionic acid (Compound 13)

Ethyl 3-[2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]ureido) propionate (Compound 111, 6.25 mmol) and K_2CO_3 (9.4 mmol) was stirred in a mixture of MeOH (25 ml) and water (8 ml) for 4 h at

ambient temperature. More water (13 ml) was added and the reaction mixture was stirred overnight. The reaction mixture was poured into EtOAc and water. pH was adjusted to approximately 4 with glacial acetic acid. The organic phase was separated, washed with water and brine, then dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a weakly coloured oily crude product. Purification was done by chromatography using CH_2Cl_2/MeOH/CH_3COOH 250:10:1 as eluant to afford the title compound.

^{13}C NMR ($CDCl_3$): δ 197.5, 176.3, 157.0, 148.9, 138.9, 137.9, 134.9, 133.5, 132.8, 131.7, 131.3, 131.1, 129.8, 128.4, 125.6, 125.5, 124.4, 123.9, 116.3, 112.6, 35.8, 34.5, 20.7, 20.5

Example 14

1-Ethyl-3-[2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]-5-fluoro-phenyl]urea (Compound 114)

General procedure: 1

Starting compound II: 2-Chloro-4-[(4-fluoro-2-aminophenyl)amino]-2'-methylbenzophenone

Starting compound III: Ethyl isocyanate

Solvent for the reaction: Pyridine

Purification: Chromatography using EtOAc/pentane 1:2 as eluant to give the title compound as an syrupy

^{13}C NMR ($CDCl_3$): δ 197.2, 162.9, 159.6, 155.1, 150.2, 138.9, 137.8, 137.4, 137.2, 135.1, 133.6, 131.4, 131.1, 129.7, 128.4, 128.0, 127.9, 125.5, 124.7, 115.6, 111.8, 110.1, 109.8, 108.2, 107.9, 35.2, 20.5, 15.1

Example 15. Tablet containing compound 103

Compound 103 (active substance)	50 mg
Lactose	125 mg
Starch	12 mg
Methyl cellulose	2 mg
Sodium carboxymethyl cellulose	10 mg
Magnesium stearate	1 mg

The active substance, lactose and starch are mixed to a homogeneous state in a suitable mixer and moistened with a 5 per cent aqueous solution of methyl cellulose 15 cps. The mixing is continued until granules are formed. If necessary, the wet granulation is passed through a suitable screen and dried to a water content of less than 1% in a suitable drier, e.g. fluid bed or drying oven. The dried granules are passed through a 1 mm screen and mixed to a homogeneous state with sodium carboxymethyl cellulose. Magnesium stearate is added, and the mixing is continued for a short period of time. Tablets with a weight of 200 mg are produced from the granulation by means of a suitable tabletting machine.

Example 16. Formulation for injection containing compound 103.

Compound 103 (active substance)	1%
Sodium chloride	q.s.
Ethanol	10%
Water for injection to make	100%

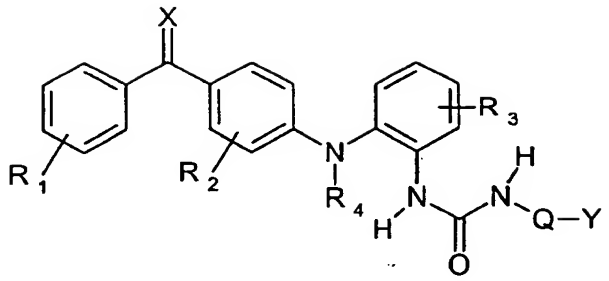
The active substance is dissolved in ethanol (10%) then water for injection made isotonic with sodium chloride is added to make 100%. The mixture is filled into ampoules and sterilized.

Example 17. Cream formulation containing compound 101.

Compound 101 (10 g) was dissolved in Octyldodecyl myristate (250g) to form Part A. Methylparaben (1 g) and propylparaben (0.2 g) were dissolved in phenoxyethanol (6 g) and mixed with a 0.025 M Phosphate buffer pH = 7.5 (632,8 g) to form Part B. Cetostearyl alcohol (50 g) and ARLACEL 165® (50 g) was melted in a vessel at 70° to 80 °C. Part A was added and heated to 60-70°C. The aqueous phase was likewise heated to 60-70 °C and slowly added to the melted oil phase under high speed stirring. The homogenized components were cooled to room temperature.

CLAIMS

1. A compound of the formula I



I

wherein R_1 represents one or more, same or different substituents selected from the group consisting of halogen, hydroxy, mercapto, trifluoromethyl, amino, (C_1-C_3)alkyl, (C_2-C_3)olefinic group, (C_1-C_3)alkoxy, (C_1-C_3)alkylthio, (C_1-C_6)alkylamino, (C_1-C_3)alkoxycarbonyl, cyano, carbamoyl, phenyl, and nitro;

R_2 represents one or more, same or different substituents selected from the group consisting of halogen, hydroxy, mercapto, trifluoromethyl, amino, (C_1-C_3)alkyl, (C_2-C_3)olefinic group, (C_1-C_3)alkoxy, (C_1-C_3)alkylthio, (C_1-C_6)alkylamino, (C_1-C_3)alkoxycarbonyl, cyano, carbamoyl, phenyl, and nitro;

R_3 represents hydrogen, halogen, hydroxy, mercapto, trifluoromethyl, amino, (C_1-C_3)alkyl, (C_2-C_3)olefinic group, (C_1-C_3)alkoxy, (C_1-C_3)alkylthio, (C_1-C_6)alkylamino, (C_1-C_3)alkoxycarbonyl, phenyl, cyano, carboxy, or carbamoyl;

R_4 represents hydrogen, (C_1-C_3)alkyl, or allyl;

Q represents a bond, -SO_2-, or -C(R_6)(R_7)(-O-C=O)-, in which formula R_6 and R_7 independently represent hydrogen, trifluoromethyl, or (C_1-C_4)alkyl;

Y represents (C_1-C_{15})alkyl, (C_2-C_{15})olefinic group, (C_3-C_{10})carbocyclic group, or phenyl, any of which is optionally substituted by one or more, same or different substituents represented by the formula R_5; or Y represents a group of formula -(Z-O)$_n$-Z, where Z is a (C_1-C_3)alkyl and n is an integer > 1, and no continuous linear sequence of atoms in the group Y exceeds 15;

R_5 represents halogen, hydroxy, mercapto, trifluoromethyl, (C_1-C_4)alkyl, amino, (C_1-C_3)alkoxy, (C_1-C_3)alkylthio, (C_1-C_6)alkylamino, (C_1-C_3)alkoxycarbonyl, cyano, azido, nitro, -COOH, -$CONH_2$, -CONHR', or -CONRR' wherein R and R' stands for (C_1-C_3)alkyl;

X represents oxygen or sulphur,

or a pharmaceutically acceptable salt thereof, or a hydrate or solvate thereof.

2. A compound according to claim 1 wherein R_1 represents one or more, same or different substituents selected from the group consisting of fluoro, chloro, bromo, hydroxy, trifluoromethyl, amino, (C_1-C_2)alkyl, (C_2-C_3)alkenyl, (C_1-C_3)alkoxy, (C_1-C_3)alkoxycarbonyl, or cyano.

3. A compound according to any one of the preceding claims wherein R_2 represents one or more, same or different substituents selected from the group consisting of hydrogen, fluoro, chloro, bromo, hydroxy, trifluoromethyl, amino, (C_1-C_2)alkyl, (C_2-C_3)alkenyl, (C_1-C_3)alkoxy.

4. A compound according to any one of the preceding claims wherein R_3 represents one or more, same or different substituents selected from the group consisting of hydrogen, fluoro, chloro, bromo, hydroxy, trifluoromethyl, (C_1-C_3)alkyl, (C_2-C_3)alkenyl, (C_1-C_3)alkoxy, (C_1-C_3)alkoxycarbonyl, cyano, or carboxy.

5. A compound according to any one of the preceding claims wherein R_4 represents hydrogen, (C_1-C_2)alkyl, or allyl.

6. A compound according to any one of the preceding claims wherein X represents oxygen.

7. A compound according to any one of the preceding claims wherein Q represents a bond.

8. A compound according to any one of the preceding claims wherein Q represents $-SO_2-$.

9. A compound according to any one of the preceding claims wherein Y represents (C_1-C_6)alkyl; (C_2-C_6)alkenyl; (C_3-C_6)cycloalkyl; (C_5-C_8)cycloalkene group; or phenyl; any of which is optionally substituted by one or more, same or different substituents selected from the group consisting of the formula R_5.

10. A compound according to the preceding claims wherein R_5 represents fluoro, chloro, bromo, hydroxy, amino, (C_1-C_2)alkoxy, (C_1-C_4)alkylamino, (C_1-C_3)alkoxycarbonyl, cyano, azido, -COOH, -$CONH_2$, -CONHR', or -CONR'R'' wherein R' represents (C_1-C_2)alkyl.

11. A compound according to any one of the preceding claims wherein R_1 represents on or more, same or different substituents selected from the group consisting of fluoro, chloro, bromo, hydroxy, methyl, or methoxy.

12. A compound according to any one of the preceding claims wherein one or both of R_1 and R_2 represent one substituent, said substituent preferably being in the ortho position.

13. A compound according to any one of the preceding claims wherein R_1 is methyl.

14. A compound according to any one of the preceding claims wherein R_2 represents one or more, same or different substituents selected from the group consisting of hydrogen, fluoro, chloro, bromo, hydroxy, methyl, or methoxy.

15. A compound according to the preceding claim wherein R_2 is Cl.

16. A compound according to any one of the preceding claim wherein R_3 represents hydrogen or fluoro.

17. A compound according to any one of the preceding claims wherein R_4 represents hydrogen.

18. A compound according to any one of the preceding claims wherein Y represents (C_1-C_6)alkyl, (C_3-C_7)cycloalkyl, or phenyl; any of which may be optionally substituted by one or more, same or different substituents selected from the group consisting of fluoro, chloro, bromo, hydroxy, amino, azido, (C_1-C_3)alkyl, (C_1-C_2)alkoxycarbonyl, cyano, -COOH, -$CONH_2$, $CON(CH_3)_2$.

19. A compound according to the preceding claim wherein Y represents methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, cyclohexyl, hexyl, 6-chloro-hexyl, $(CH_2)_2COOCH_2CH_3$, $(CH_2)_2COOH$, tolyl, or phenyl.

20. A compound according to claim 1 selected from the group consisting of
1-Cyclohexyl-3-[2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]urea (Compound 101),
1-Ethyl-3-[2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]urea (Compound 102),
1-[2-[3-Chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]-3-phenylurea (Compound 103),
1-Butyl-3-[2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]urea (Compound 104),
1-[2-[3-Chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]-3-(4-methylphenylsulfonyl)urea (Compound 105),
1-[2-[3-Chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]-3-(phenylsulfonyl)urea (Compound 106),
1-*tert*-Butyl-3-[2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]ur a (Compound 107),

1-[2-[3-Chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]-3-*iso*-propylurea (Compound 108),
1-[2-[3-Chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]-3-propylurea (Compound 109),
1-Methyl-3-[2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]urea (Compound 110),
Ethyl 3-[2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]ureido)propionate (Compound 111),
1-Ethyl-3-[5-bromo-2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]urea (Compound 112),
3-[2-[3-Chloro-4-(2-methylbenzoyl)-phenylamino]phenyl]ureido)propionic acid (Compound 113),
1-Ethyl-3-[2-[3-chloro-4-(2-methylbenzoyl)-phenylamino]-5-fluoro-phenyl]urea (Compound 114),
and salts thereof with pharmaceutically acceptable acids, hydrates and solvates.

21. A pharmaceutical composition containing as an active ingredient a compound according to any one of claims 1 to 20 together with a pharmaceutically acceptable carrier and optionally together with a second active ingredient optionally selected from the group consisting of glucocorticoids, vitamin D's, anti-histamines, platelet activating factor (PAF) antagonists, anticolinergic agents, methyl xanthines, β-adrenergic agents, salicylates, indomethacin, flufenamate, naproxen, timegadine, gold salts, penicillamine, serum cholesterol-reducing agents, retinoids, zinc salts, and salicylazosulfapyridin (Salazopyrin).

22. A pharmaceutical composition according to the preceding claim wherein the active ingredient comprises from 0.1% to 100% by weight of the composition.

23. A pharmaceutical preparation according to claim 21 or 22 in unit dosage form containing between 0.07 mg and 1 g of the active ingredient.

24. Use of a compound according to any one of claims 1 to 20 for the preparation of a medicament.

25. Use of a compound according to any one of claim 1 to 20 for the preparation of a medicament for the treatment and/or prophylaxis of asthma, allergy, arthritis, including rheumatoid arthritis and spondyloarthritis, gout, atherosclerosis, chronic inflammatory bowel disease (Crohn's disease), proliferative and inflammatory skin disorders, such as psoriasis, atopic dermatitis, uveitis, septic shock, AIDS, osteoporosis and acne.

26. A method for the treatment and/or prophylaxis of asthma, allergy, arthritis, including rheumatoid arthritis and spondyloarthritis, gout, atherosclerosis, chronic inflammatory bowel disease (Crohn's disease), proliferative and inflammatory skin disorders, such as psoriasis, atopic dermatitis, uveitis, septic shock, AIDS, osteoporosis and acne, characterised in administering to a patient suffering from at least one of said diseases an effective amount of one or more compounds according to any one of claims 1 to 20 as an active ingredient alone, or if necessary together with a pharmaceutically acceptable carrier, and, optionally, a second active ingredient optionally selected from the group consisting of glucocorticoids, vitamin D's, anti-histamines, platelet activating factor (PAF) antagonists, anticolinergic

agents, methyl xanthines, β-adrenergic agents, salicylates, indomethacin, flufenamate, naproxen, timegadine, gold salts, penicillamine, serum cholesterol-reducing agents, retinoids, zinc salts, and salicylazosulfapyridin (Salazopyrin).

27. A method of treatment according to the preceding claim comprising administering to a mammal in need of systemic treatment a suitable dose of a compound of formula I of from 0.1 to 200 mg/kg bodyweight, preferably a dose of from 0.2 to 50 mg/kg of mammal bodyweight one or more times daily.